Childhood-Onset Schizophrenia: Brain MRI Rescan After 2 Years of Clozapine Maintenance Treatment

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Objective: *The effect of clozapine on striatal morphology was examined in adolescents with childhood-onset schizophrenia.* *Method:* *Eight adolescent patients with onset of psychosis before age 12 and eight matched comparison subjects had initial and 2-year follow-up brain magnetic resonance imaging scans. Basal ganglia and lateral ventricle volumes were measured. The patients were on a clozapine regimen during the 2-year interim.* *Results:* *Caudate volume was larger in the patients at the initial scanning, decreased in the patients between scans, and did not differ significantly between the patients and the comparison subjects at the second scanning.* *Conclusions:* *Caudate enlargement in patients with childhood-onset schizophrenia who are taking typical neuroleptics appears to be secondary to medication exposure. Rescanning to examine basal ganglia morphology is indicated for these patients when they are taking an atypical neuroleptic.*

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Several magnetic resonance imaging (MRI) brain morphologic studies (1–7) and one neuropathological study (8) have found increased basal ganglia volumes (caudate, putamen, and globus pallidus) in adults with schizophrenia. While the etiology of enlarged basal ganglia is unclear, growing evidence suggests that chronic treatment with typical neuroleptics may be responsible, leaving obscure the relationship to disease process (2, 3, 6). Keshavan et al. (2) found increased caudate volume in 11 previously treatment-naive schizophrenic patients when they were treated with typical neuroleptics. Chakos et al. (3) found caudate volumes decreased in eight schizophrenic subjects first scanned while receiving typical neuroleptics and then while receiving clozapine maintenance treatment; there was caudate enlargement in a contrast group who continued treatment with typical agents. The data of Chakos et al. suggest that dopamine D_2 receptor effects of typical neuroleptics may be responsible for enlarged basal ganglia.

In a systematic brain MRI study of 21 patients with childhood-onset schizophrenia chronically treated with typical neuroleptics (9), our group found brain abnormalities similar to those seen in adults, including significantly smaller brain volume and a trend toward enlarged lateral ventricles. We also found robust increases in basal ganglia volume ($p=0.05$ for the caudate, $p=0.007$ for the putamen, and $p=0.0002$ for the globus pallidus according to analysis of covariance with total cerebral volume as the covariate).

As part of a clozapine treatment trial (10), eight of these patients with childhood-onset schizophrenia and eight matched comparison subjects had 2-year follow-up scans to examine changes in basal ganglia. We hypothesized that basal ganglia volume would decrease for our patients who were maintained on a regimen of clozapine during the 2-year interim. In addition, because a recent follow-up study (11) showed a differential increase in ventricle volume over time, we further speculated that our early-onset group, with a possibly more pronounced brain insult, might be likely to show such progression.

METHOD

Patients aged 6–18 years who had treatment-refractory schizophrenia, diagnosed according to DSM-III-R, and who had a full-scale IQ of 70 or above were recruited nationally for a double-blind comparison of haloperidol and clozapine (10). Eight patients (seven male and one female) had two MRI scans, the first while they were inpatients and the second at 2-year follow-up. The mean age of this group on admission to the National Institutes of Health was 15.1 years

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(SD=2.3); their mean age at onset of psychosis was 10.5 years (SD=1.3). The mean duration of typical neuroleptic therapy before the first scan was 24.8 months (SD=19.4). All eight patients were taking clozapine at the time of the second scan (mean dose=400 mg/day, SD=128.9, range=200–600). Two patients were taking clozapine only; six were taking one or two concomitant psychotropic medications, including fluoxetine, valproic acid, and haloperidol (only one patient was taking haloperidol, 1 mg/day).

Eight comparison subjects (mean age=15.4 years, SD=3.1) matched for age, sex, and handedness also had scans. There was no difference between the group of patients and the comparison group in height, weight, or Tanner stage. Screening procedures for the comparison subjects have been reported elsewhere (9, 12). At 2-year rescan, comparison subjects had no change in medical, neurologic, or psychiatric status.

Assent was obtained from the adolescents and written informed consent from the parents. The protocol was approved by the institutional review board of the National Institute of Mental Health.

Identical scanning methodology and the same scanner were used for the initial scanning and the rescanning, as described elsewhere (9, 12, 13). A General Electric 1.5-T Signa scanner with a three-dimensional spoiled gradient imaging sequence (TE=5 msec, TR=24 msec, flip angle=45°, acquisition matrix=192×256 pixels, number of excitations=1, field of view=24 cm) was used to obtain T_1-weighted images with a slice thickness of 1.5 mm in the axial plane and 2.0 mm in the coronal plane.

Neuroradiology reports indicated a focal increased signal in the left frontal white matter of one schizophrenic patient at time 1 and a probable small cranial fossa arachnoid cyst in another patient at time 2.

The image analysis technique is described elsewhere (9, 12). Motion artifact prevented subcortical measurements for one patient.

Methods of measurement are also described elsewhere (9, 12). Imaging was done blind to diagnosis and time of scan. Intraclass correlation coefficients ranged from 0.84 to 0.99 (12).

To examine differences between the patients and comparison subjects at times 1 and 2, t tests and two-way (diagnosis by time) repeated measures analysis of variance were used. Given our hypotheses, the p values reported for these follow-up data are one-tailed.

RESULTS

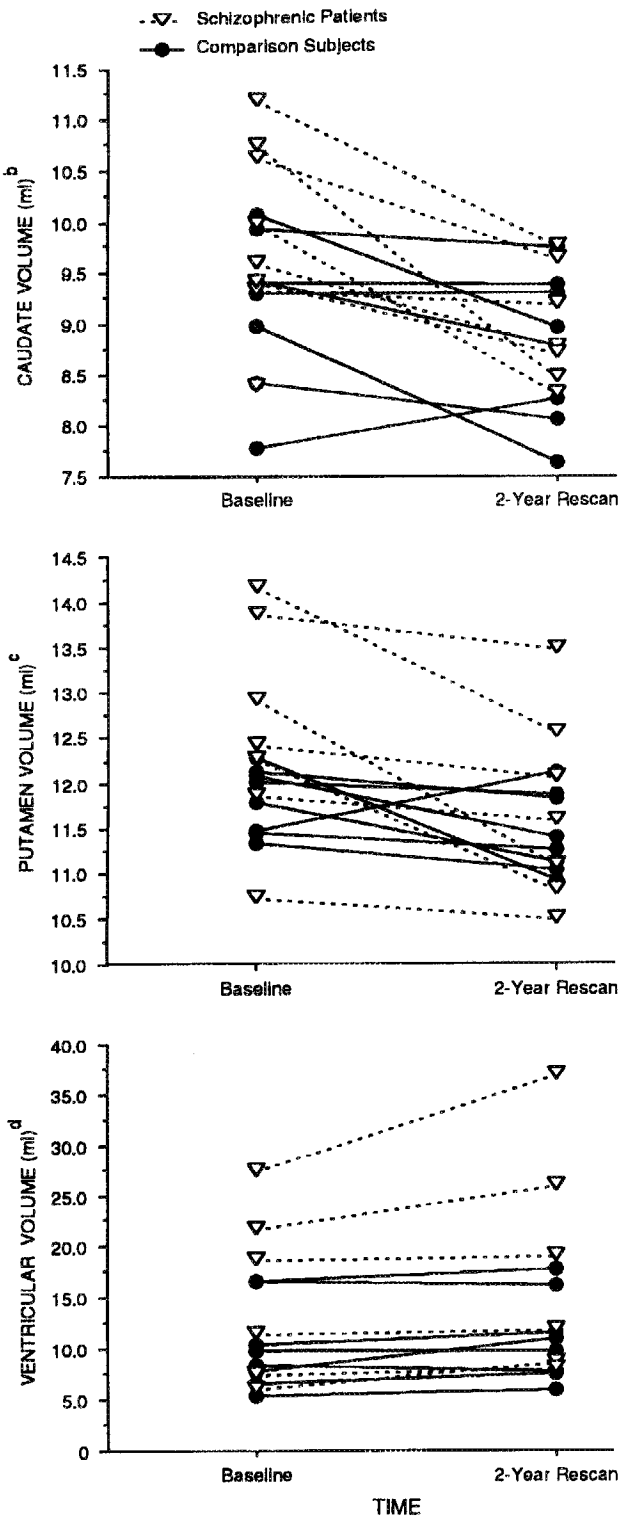
At time 1, in this subset of follow-up patients with childhood-onset schizophrenia, the mean volume of the caudate was larger than that of the comparison subjects (t=1.75, df=14, p=0.05). There was no significant difference between the groups in the volume of the putamen, globus pallidus, or ventricles at time 1.

The patients had a decrease in caudate volume between scans 1 and 2 as compared to the comparison subjects (figure 1). Of note, at time 2 there was no difference in caudate volume between the two groups. Similarly, the putamen decreased in volume over time in the patients; however, the difference did not reach statistical significance (figure 1). The globus pallidus decreased equally in both groups (for time, F=21.74, df=1, 13, p=0.0002). The volume of the lateral ventricles increased in the patients, but this difference did not reach statistical significance (figure 1).

There was no significant correlation between changes in ventricle volume and volumes of the caudate and the putamen.

Clinically, all patients, even the two with relative ventricle enlargement from scan 1 to scan 2, continued to show some improvement while taking clozapine during the 2-year interval.

FIGURE 1. Caudate, Putamen, and Ventricle Volumes of Patients With Childhood-Onset Schizophrenia (N=7) and Matched Comparison Subjects (N=8) at Baseline and at 2-Year Follow-Up[a]



[a]All patients were maintained on clozapine treatment during the 2-year interim.
[b]Analysis of variance (diagnosis by time): F=4.96, df=1, 13, p=0.02.
[c]Analysis of variance (diagnosis by time): F=2.32, df=1, 13, p=0.08.
[d]Analysis of variance (diagnosis by time): F=2.38, df=1, 13, p=0.07.

DISCUSSION

To our knowledge, this is the first brain MRI rescan study of adolescents with childhood-onset schizophrenia. In our small study group we replicated the finding of Chakos et al. (3) of a decrease in caudate volume during clozapine maintenance treatment. Our data extend this finding by suggesting a similar result for the putamen, although our numbers were too small to reach significant conclusions. Unexpectedly, the globus pallidus decreased in both the patients and the comparison subjects; this is puzzling, as our cross-sectional normative data do not indicate morphologic change in this structure in this age range (12).

Presumably, the drug-related increase in caudate volume at time 1 was secondary to the medication effect of typical agents. Microscopic effects of typical neuroleptics have been found in the rat corpus striatum (14, 15), with normalization upon medication washout (15). The decrease in caudate volume in our patient group during clozapine treatment suggests that future imaging studies of early-onset patients treated with atypical agents may allow for clearer study of basal ganglia development in childhood-onset schizophrenia.

Although not statistically significant, and based on only two subjects, there was a potential finding of differential ventricle enlargement in our group with childhood-onset schizophrenia (figure 1). While one of these subjects was unremarkable with respect to demographic characteristics and history, the second subject was the child of a mother with many obstetrical complications. This subject also presented premorbid features of pervasive developmental disorder. A prospective 4-year rescan MRI study of 20 first-episode patients (11) found increased ventricle volume in contrast to five comparison subjects. While our possible finding of increased ventricle volume over time is based on two individuals, rescan of a larger group would be of great interest to determine whether our childhood-onset schizophrenia group has a greater proportion of these cases and may provide more clues about the nature of the disorder (neurodegenerative versus neurodevelopmental). We are increasing the number of rescans to address this question further.

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